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Clinical Experience with ALG

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There will be little point in dwelling on our clinical experience with ALG, extensive though this has been. The reason is that we have not carried out a contemporaneous control study omitting ALG. We do not have, as a consequence, proof that our results were improved by the clinical introduction of ALG. Nevertheless, there is evidence supporting this point of view which we will briefly describe.

Related Transplantations

Our first renal homotransplantations were carried out in 1962. If related donors could be found, substantial benefits for the majority of recipients were obtained from the very beginning of our experience.

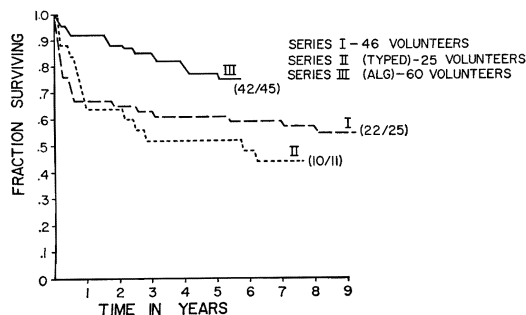


Fig. 1

Life survival curves of 3 groups of recipients of consanguineous kidneys. The patients in Series I were treated with the double drug program of azathioprine and prednisone from 1962 to March, 1964 and, consequently, have potential follow-ups of 8 to 9½ years. The patients of Series II were treated from October, 1964 to April, 1966 and, consequently, have potential follow-ups of 6 to 7½ years. They received the same drug therapy as in Series I and, in addition, an attempt was made at donor selection by HL-A matching. The recipients of Series III were treated with the triple drug program of azathioprine, prednisone, and ALG between June, 1966 and April, 1968; they have potential follow-ups of 4 to 6 years. In all 3 series, the denominator indicates the surviving patients whereas the numerator tells the number of originally transplanted kidneys that are still functioning in those survivors.

In Fig. 1 is shown graphically the fate of 131 consecutive patients who were given kidneys by siblings, parents, or more distantly related donors such as aunts, uncles or cousins between 1962 and the spring of 1968. The follow-up in Series I is now 8 to 9½ years, in Series II from 6 to 7½ years, and in Series III from 4 to 6 years.

The 71 patients of Series I and II were treated with azathioprine and prednisone. Tissue typing techniques were not used in Series I since they were not yet available. In Series II, an effort was made by Dr. P. Terasaki to select the best donor amongst those available in any given case. This effort of donor discrimination was not beneficial (Fig. 1) and, in fact, the eventual survival was somewhat inferior to that in Series I.

The 60 patients of Series III were administered horse antilymphocyte globulin (ALG) in addition to azathioprine and prednisone. With minimum of follow-ups of at least 4 years, the survival of both patients and grafts appears to have been increased (Fig. 1). Even today, after 4 to 6 years, 75% of these ALG treated patients are still alive and all but 3 of the survivors (42 of 45) have acceptable function of their original homografts.

Generally, the ALG treated patients had globulin therapy for about 4 months post-transplantation, with intramuscular injections of 3 to 6 mg/kg. The ALG was started several days before operation and given daily for 2 weeks, every other day for 2 weeks, twice a week for 2 months and once a week for a final month. Because they were the only available source of human lymphoid tissue in large quantities, human spleens were used in this era to raise the ALG with careful attention being paid to separating the leukocytes from stroma, platelets and red cells before their inoculation into horses. After absorption and purification the eventual product usually had

lymphocytotoxic and leukoagglutinin titers of 1:4000 or preferably greater. Anti-GBM activity was not demonstrable in the Dixon rat model.

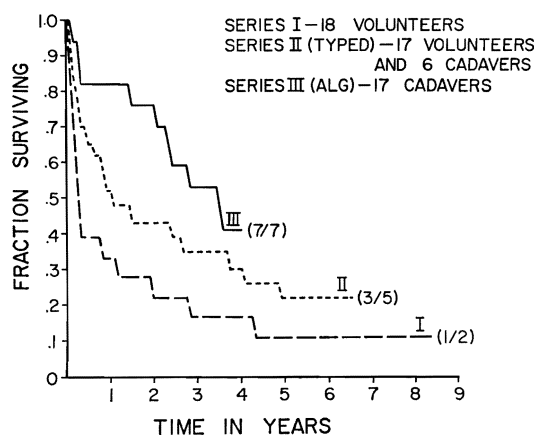


Fig. 2

The results after transplantation of non-related kidneys. The conditions of treatment and the meaning of the figures in the parenthesis are identical to those in Fig. 1. Note that the results with non-related kidneys have been inferior to those with related grafts at all levels of our experience. The follow-ups are also the same as in Fig. 1 except in Series III, in which the potential follow-ups are 3 to 6 years.

Non-Related Homografts

As with the consanguineous cases, the introduction of ALG as part of a triple drug treatment program was associated with an improvement in results. This is demonstrated in Fig. 2, in which Series I and II conform to the same intervals defined in the preceding section, and in which Series III is also comparable except that cases were included through April, 1969. In the 1962–1966 era, the patient survival rate at one year was between 33 and 52%. In Series III, this one year figure rose to 82% (14 of 17 patients). After one year, in all 3 series, including the final ALG group, the ultimate survival has drifted off far more rapidly than with the use of related homografts.

Is There an Indispensable Drug?

Subsequent to the completion of Series III, and continuing until February, 1971, more than 160 additional patients were given either related or cadaveric renal homografts under immunosuppressive therapy with azathioprine, prednisone, and ALG. In a general way, the results were confirmatory of those in Series III, although the survival was not quite so high, primarily because the medical criteria for acceptance to the program were so drastically relaxed. Finally, for more than a year cyclophosphamide has been used in place of azathioprine in a triple drug program that includes steroids and ALG. Here, too, the results have been good, both in related and non-related cases.

In reviewing our experience of the last decade as we have just briefly done, the point can be made that the one absolutely indispensable agent that has made renal transplantation practical is prednisone. More than occasional successes are possible with the omission of either one or 2 of the three other major agents we have mentioned, namely azathioprine, cyclophosphamide or ALG. However, without adrenal corticosteroids, we believe that the management and reversal of rejection would be so seldom achievable that the clinical discipline of renal transplantation would vanish.

It is in this context that ALG must be evaluated. We have always considered ALG to be an adjuvant immunosuppressant, and one which is of the greatest value for short-term use during the often difficult early postoperative period when the issue of graft acceptance or failure is most commonly decided. When used in this way, rather than as a panacea, we have been convinced that ALG is an important part of our therapeutic armamentarium and one that has not only improved survival but also the quality of convalescence. Improvements in the raising and standardizing of our ALG have been described at another session by Dr. C. Groth; (this issue; page 86).